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# Evaluation of efficacy and safety of intradermal PPD for treating facial warts - A prospective study

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ABSTRACT

**Introduction:** Commonly used destructive treatment modalities for treatment of warts though effective, are associated with pain, pigmentary changes, scarring and recurrences. Utilization of various vaccines and skin test antigens has broaden the horizon of available immunotherapeutic armamentarium for the treatment of warts.
**Aim:** Evaluation of efficacy and safety of intradermal PPD for treating facial warts - a prospective study..
**Materials and Methods:** Fifty-four patients with facial warts were treated with intradermal injections of PPD 10 TU/0.1 ml at two weekly intervals. They were followed up at 2, 4, 6, 8, and 12 weeks for assessment of response, adverse effects and recurrence of facial warts.
**Results:** Out of 54 (M: F 25:29) patients, only 49 patients with facial warts completed the study. Overall, complete clearance in 22(45%) patients and partial clearance in 18(37%) patients were observed. The patients with complete/partial clearance were highly satisfied from the treatment. Recurrence was not seen in our patients. Few patients had injection site pain for 2-3 days not warranting discontinuation of treatment. Other adverse effects included temporary erythema and swelling in 3 patients which subsided on its own in 2-3 days.
**Conclusion:** 82% patients responded (complete and partial response) to therapy. Intradermal PPD appears effective, safe, and acceptable treatment modality for facial warts. It carries the advantage of patient compliance, insignificant adverse effects and high patient satisfaction.



## 1. Introduction

Warts are caused by human papilloma virus (HPV) infection of fully differentiated epithelium of skin and mucous membrane. Over 100 HPV types have been recognized having an affinity for different body sites. Plane or flat warts (verruca plana), caused by HPV types 3 or 10, are round or polygonal flat topped papules, usually of skin colour or may sometimes be pigmented and vary in size from 1 to 5 mm. They usually occur in children on the distal limbs and face. The most common indications for the treatment of cutaneous warts include pain, functional impairment, cosmetic reasons, and the risk of malignancy. Warts on cosmetically important areas such as face and hands may affect patient's quality of life.[1] They can be a cause of social embarrassment, fear of negative appraisal by peers, and frustration due to their persistence and recurrence. Removal of warts by ablative therapies is often painful and frequently leads to scarring and recurrence.[2–5]

Immunotherapy is defined as a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.[6] Treatment with immune modulators such as topical contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimitidine, or zinc sulphate has been tried with variable success.[7–10] Utilization of various skin test antigens like candida, mumps, tuberculin and vaccines such as Bacillus Calmette-

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Guérin (BCG) vaccine, mumps measles rubella vaccine and Mycobacterium w vaccinehas broadened the horizon of available immunotherapeutic armamentarium for the treatment of warts. [11–17]

PPD (Purified Protein Derivative or Tuberculin) is a sterile protein extract from culture of mycobacterium tuberculosis. It is used in skin testing to detect exposure to the bacillus. It stimulates the cell-mediated immunity non-specifically by activating NK cells, Th1 cells and cytokine production. An increase in IL-12 as a part of the enhanced cell mediated immunity contributes to its mechanism of action as an immunotherapeutic agent. [18]

Immunotherapy is an encouraging therapeutic modality for the treatment of recurrent and resistant warts which augments the immune response against the causative agent thereby leading to complete resolution and decreased recurrence without any visible changes or scarring. As there is paucity of data on efficacy of intradermal PPD in treatment of facial warts, we intended to carry out this study in patients of facial warts to see the efficacy of intradermal PPD.

## 2. Materials and Methods

The study was conducted at Dr. Rajendra Prasad Government Medical College and hospital, Kangra at Tanda (Himachal Pradesh, India) after obtaining clearance from institutional ethical committee. Fifty two consecutive patients with facial warts were enrolled in the study regardless of duration and number of warts or previous treatments. Pregnant and lactating women, children $\leq$1 5 years, patients with immunosuppression were excluded. Clinical details regarding age, gender, duration and number of warts were recorded for each patient. Pre procedure counseling was done for each patient regarding details of procedure, potential benefits and possible immediate side effects over injection site.

### *2.1. Treatment protocol*

0.1 ml PPD containing 10TU was injected intradermally in the middle third of forearm with 30 G insulin syringe after cleaning the site with70% alcohol or denatured spirit. Patients were followed regularly for clinical assessment and treatment was repeated at 2 week interval till complete resolution of all warts or a maximum of five injections in cases of partial clearance or no improvement. The patients were asked to return for follow up at 12 weeks study period to assess the final outcome or any recurrence.

### *2.2. Evaluation for therapeutic outcome*

All patients were evaluated for therapeutic outcome measured as the reduction in size or number of warts during follow-up visits at 2 weeks, 4 weeks, 6 weeks, 8 weeks and 12 weeks. Pre and post treatment photographic comparison was also made to assess and corroborate the therapeutic response. The clinical response was graded as shown in Table 1. Subsequently patients were advised to report any time in case of recurrence.

At each visit, patients were enquired about the occurrence of any systemic or local adverse reactions such as pain during and after treatment, erythema or swelling at injection site, pigmentary changes, fever and any other associated complaints.

## 3. Results

Baseline characteristics of study patients are depicted in Table 2. Out of 54 patients, 49 completed the study which included 23 men and 26 women (M: F = 0.88:1) aged between 18 and 55(34.5$\pm$14.1) years. Five patients did not complete the study two were lost to follow up after the first dose and one each left after the second, third and fourth dose without assigning any particular reason. These patients were excluded from the final analysis. The duration of warts was 1 month to 3 years (16.4$\pm$8.3 months). The number of warts varied between 6-26 and the majority, 36 patients had $>$10 warts.

Table 3 shows clearance of warts at second, third, fourth, eighth week and at the end of 12 week study period. Overall 22 (44.9% ) patients showed complete clearance of warts and partial clearance was seen in 18 (36.7%) patients at the end of 12 weeks study period. Complete clearance of warts was observed after second session in 5patients, 6 patients after third session, 5 patients after fourth session and 6 after fifth session at 4 weeks, 6weeks, 8 weeks and 10 weeks respectively (Figures 1, 2 and 3).

At the end of study period, partial response was seen in 18 patients. Nine (18.4%) patients did not show any response on completion of treatment. A complete or partial response was observed in 40(81.6%) patients treated with intradermal PPD. No patient with facial warts showed recurrence at the end of 12-week study period.

Intradermal PPD injection was tolerated well by all the patients. A few patients had injection site pain for 2-3 days not warranting discontinuation of treatment. Other adverse effects included temporary erythema and swelling in three patients which subsided of its own in 2-3 days. No other systemic adverse effects occurred in any patient.

**Table 1:** Grades of improvement

| Grades | Definition |
|---|---|
| Complete clearance | Complete disappearance of warts and skin texture at the site is restored to normal |
| Partialclearance | Residual after 12 weeks |
| No change | No change in size and texture |

**Table 2:** Baseline profile of patients

| Baseline characteristics | Number of patients (%) |
|---|---|
| **Gender** | |
| Males | 25 (46.3%) |
| Females | 29 (53.7%) |
| M:F | 0.86:1 |
| Age (Years) | |
| Range | 18-55 |
| 18-30 | 30 (55.6%) |
| 31-40 | 18 (33.3%) |
| >40 | 6 (11.1%) |
| Mean±SD | 34.5±14.1 |
| **Duration of warts (Months)** | |
| Range | 1 month- 3 years |
| <6 | 20 (37.1%) |
| 6-12 | 24 (44.4%) |
| >12 | 10 (18.5%) |
| Mean±SD (months) | 16.4±8.3 |
| **Number of warts** | |
| Range | 6-26 |
| Mean | 16.87 |

**Table 3:** Response to therapy

| | Complete Clearance |
|---|---|
| First dose | 0 |
| Second dose | 5 |
| Third dose | 6 |
| Fourth dose | 5 |
| Fifth dose | 6 |
| At the end of the study | 22 |

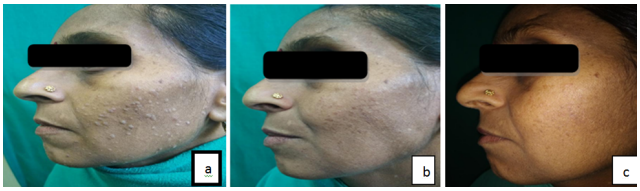


**Fig. 1:** Response to therapy; a) multiple warts before treatment; b) Response to PPD after 2 doses; c) complete clearance after 3 doses

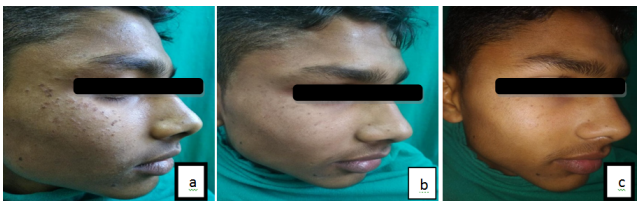


**Fig. 2:** Response to therapy; a) multiple warts before treatment; b) Response to PPD after 2 doses; c) complete clearance after 3 doses

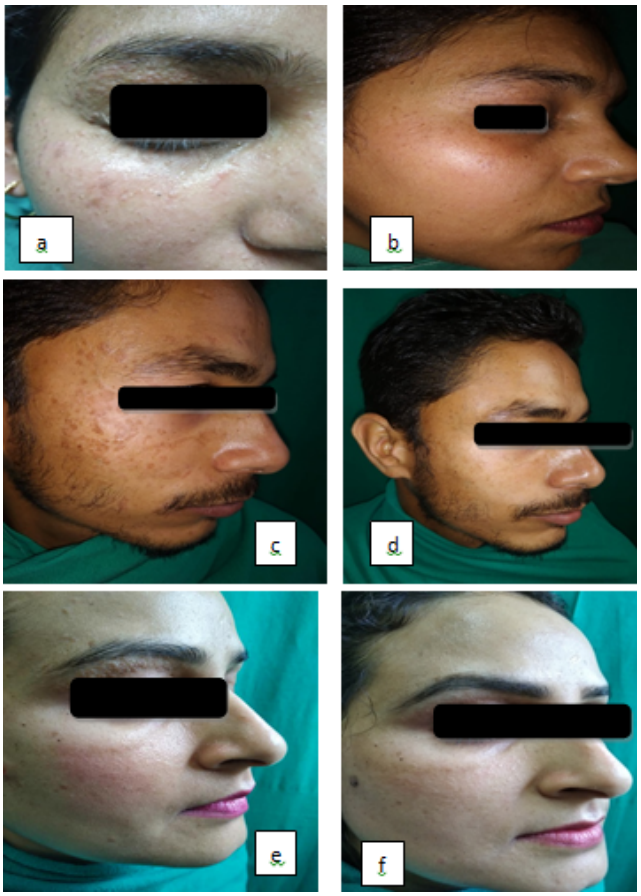


**Fig. 3:** Response to therapy; (a, c and e) multiple warts before treatment; (b, d, and f)complete clearance after 2 doses

## 4. Discussion

Facial warts are otherwise asymptomatic and patients seek treatment mainly due to cosmetic disfigurement caused by the multiple lesions. Destructive methods are commonly used for the treatment of facial warts which are painful and always pose a risk of scarring and pigmentation. Immunotherapy is considered quite beneficial for plantar, facial and genital warts as they have been found to regress without any scarring.[19–21] Additionally, the recurrence rate following immunotherapy is negligible as compared to destructive procedures,[17,20,22] Immunotherapy using various bacterial, fungal and viral antigens as a treatment modality for warts has been used in various studies with good results without scarring. Injection of PPD augments the cell mediated immunity comprehensively through activation of Th1 cytokines, natural killer cells and cytotoxic T cells that stimulates a strong immune response against all types of warts such as verruca plana, verruca vulgaris and plantar warts irrespective of the serotype of HPV.[12,20,21] It is especially promising in countries where vaccination against tuberculosis is routinely done.[23]

PPD for treatment of warts has been used intradermally, topically as well as intralesionally. In our study, we observed complete clearance of warts in 22 (44.9%) patients while partial response was seen in 18(36.7%) patients at the end of 12 weeks. Response was seen as early as at two weeks after the first injection in five patients. Lahti and Hannuksela[24] in their study observed a low clearance rate of 57% with topical tuberculin jelly at 3-4 months. The disappearance of warts usually occurred in the $3^{rd}$ and $4^{th}$ months. In comparison to PPD immunotherapy, the major disadvantage of topical tuberculin jelly was the longer duration of treatment. Therefore intradermal PPD is a better mode of treatment for multiple warts for earlier and higher clearance. Abo Elela et al reported a complete clearance rate of 96% after ten injections of intradermal PPD as compared to 94.1% when PPD was used intralesionally.[12] Nimbalkar et al[13] in their study of 45 patients having viral warts observed that 62.2% of their patients showed complete clearance at injected and distant warts while 17.8% showed partial clearance. They had injected 10 TU of tuberculin PPD (0.1 ml) intralesionally in the largest wart at 2 weekly intervals to a maximum of six treatment sessions. Saoji et al in another study injected 2.5 TU of PPD intralesionally in a few warts with a total of four sessions at 2 weekly intervals and observed a complete disappearance of warts in 76% of patients respectively.[14] Podder et al in their study used intradermal PPD to treat 27 patients and observed a complete clearance in 18.52% while others had partial response at 12 weeks.[25]

Immunotherapy addresses the limitations of surgical/destructive therapies. It enhances the cell mediated immune response that clears the virus infective tissue irrespective of whether it is visible or not. So there are lesser chances of recurrence. It also targets warts situated away from the site of the immunotherapeutic injection and therefore help in treating warts on inaccessible sites and on cosmetically important areas where ablative therapy cannot be done due to patients apprehension or scarring thereof.[25]

PPD immunotherapy was well tolerated by our patients. Mild injection site pain was the most common adverse effect. Other adverse effects included temporary erythema and swelling in three patients which subsided of its own in 2-3 days.

Tuberculin PPD was found to be an effective, well tolerated therapeutic modality for treatment of multiple facial warts with minimal side effects. It is easily available, pocket-friendly to the patient and easy to use. In case of facial warts due to cosmetic reasons surgical or destructive procedures are generally avoided. Intradermal injection on other hand can be safely given and there is minimal pain and scarring.

## 5. Conclusion

The study shows that intradermal PPD is an effective and safe option to treat facial warts with high patient satisfaction. No significant systemic adverse effects noted. The intradermal injection does not require special puncture needles or technical expertise and there is minimal drug wastage. Non-responders/partial responders may require more number of doses (>5), and further follow-up is required in the patients with partial responders.

## 6. Limitations

Smaller number of patients, lack of control group and short follow up are main limitations of this study.

## 7. Conflict of Interest

All authors declare that they have no conflict of interest.

## 8. Financial Disclosure

None.

## 9. Ethical Approval

Approved from Institutional ethics Committee.

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